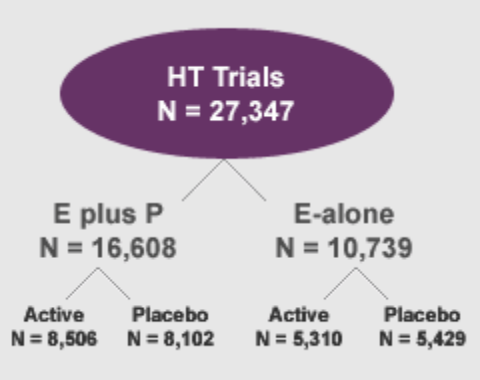
WHI Hormone Therapy Trials Overview

Background

Prior to the WHI, observational studies suggested that postmenopausal hormone therapy was associated with a decreased risk of coronary heart disease. Other research findings indicated that hormone therapy was also associated with a decreased risk of osteoporosis and increased bone density, although the effects of hormone therapy on actual fracture incidence had not been determined. The WHI Hormone Therapy Trials (HT) were designed to test the effects of postmenopausal hormone therapy on women's risk for coronary heart disease and hip fractures (primary analyses) and other fractures and breast cancer (secondary analyses). The effects of hormone therapy on endometrial cancer was also evaluated in women with a uterus.



Screening and Eligibility

In addition to the general Clinical Trial exclusion criteria, HT-specific eligibility criteria were focused on safety (e.g., no history of hypertriglyceridemia or endometrial cancer, normal mammogram) and adherence (e.g., willingness to be randomized to active or placebo arms). All participants who were eligible for and interested in the HT were dispensed a 28-day supply of placebo study pills for an enrollment (run-in) trial, which could be repeated once. An adherence of 80% or greater during the enrollment period was required for eligibility.

Baseline Characteristics

The HT consisted of two separate clinical trials in postmenopausal women ages 50 to 79 years at baseline—a trial of combined estrogen and progestin (Estrogen plus Progestin or E+P) in women who had an intact uterus at baseline (n=16,608) and a trial of estrogen (Estrogen Alone or E-Alone) in women who had a prior hysterectomy at baseline (n=10,739). When the WHI began in 1993, women with a uterus were also randomized to unopposed estrogen or a placebo, but those participants assigned to active treatment were reassigned to combined estrogen plus progestin in early 1995. Baseline characteristics of participants in E+P and E-Alone trials are available in the HT baseline monograph.

Early Stopping

Following a WHI Data and Safety Monitoring Board (DSMB) review of the cumulative data to date, the E+P trial was stopped early in July 2002, after an average of 5.6 years of follow-up. The DSMB determined that combined estrogen plus progestin was associated with an increased risk of breast cancer, some increased risk of cardiovascular disease, and more harm than benefit overall. The Estrogen-Alone trial was stopped early in March 2004, after an average of 7.1 years of follow-up, because an increased risk of stroke was found with no benefit for coronary heart disease. The National Institutes of Health determined that follow-up for the remaining years would not change these overall findings and it would not be appropriate to expose healthy women to this risk in a prevention trial.

Estrogen plus Progestin Trial

Participants with an intact uterus at baseline were randomized in a 1:1 fashion to one of two arms:

- Combined hormone therapy, consisting of 0.625 mg of conjugated equine estrogens plus 2.5 mg of medroxyprogesterone acetate daily (Prempro, Wyeth Ayerst, Philadelphia, PA)
- Daily placebo pill

Estrogen-Alone Trial

Participants with a history of hysterectomy at baseline were randomized in a 1:1 fashion to one of two arms:

- Unopposed estrogen therapy, consisting of 0.625 mg of conjugated equine estrogens (Premarin, Wyeth Ayerst, Philadelphia, PA)
- Daily placebo pill

Follow-Up Data Collection

Hormone Therapy Trial participants were followed up six weeks after randomization to address management (e.g., symptoms and adherence) and safety issues and then semi-annually for health-related outcomes and management and safety issues. Clinic visits were conducted annually, during which additional physical and gynecological examination data were collected and reviewed for safety concerns. HT participants were also required to have annual mammograms, and study pills were not dispensed if a benign mammogram report had not been received in the previous 18 months. If symptom or safety concerns (e.g., vaginal bleeding, breast changes) or adherence challenges (e.g., difficulty remembering to take study pills) were noted, these concerns were evaluated and addressed during participant contacts by trained clinicians and followed-up as appropriate.

Symptom Management

Participants were advised on self-care strategies for managing symptoms. A detailed algorithm for managing vaginal bleeding in the E+P trial was developed and was included in the HT section of the staff procedures manual (below) and a consulting gynecologist's handbook that included excerpts of study procedure and forms. Strict safety criteria were defined for unblinding a participant's treatment arm, with only the clinic's consulting gynecologist being unblinded, as necessary, to manage bleeding. Briefly, no intervention was required during the first 6 months after randomization if vaginal bleeding was equal to or lighter than a regular menstrual period. For heavier bleeding at 6 months or for bleeding after 6 months, algorithms focused on the severity of bleeding, time since randomization, study arm assignment, and endometrial pathology (of endometrial aspiration or transvaginal uterine ultrasound). Additional "open-label" estrogen or progestin, referral to a personal health care provider, or discontinuation of study pills were ordered based on these specific protocols, with re-evaluation in 6 months, as appropriate.

Protocol-Mandated Reasons for Discontinuing Study Pills

HT study pills were discontinued temporarily or permanently, without unblinding treatment arm, for participants who developed certain health conditions (e.g., breast cancer, endometrial cancer) or began taking certain prescription medications (e.g., hormone therapy, selective estrogen receptor modulators).